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CLINICAL SPECTRUM OF NEUROSARCOIDOSIS

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ABSTRACT Sarcoidosis is a multi-system granulomatous disease of unknown etiology. CNS complications occur in 5-10% of patients with sarcoidosis. Neurosarcoidosis should be considered in patients with known sarcoidosis who develop neurological complications and in patients who present with findings consistent with neurosarcoidosis. In this case series we present 4 cases of neurosarcoidosis presenting as multiple cranial neuropathies, myelopathy and in association with myasthenia gravis.

KEYWORDS : neurosarcoidosis, myelitis, cranial neuropathy

INTRODUCTION:

Sarcoidosis is a multisystem granulomatous disease of unknown etiology(1). The incidence of sarcoidosis is 1-40/100000 people and varies with ethnicity(2). Neurosarcoidosis can affect practically any part of the neuro axis(3). CNS complications occur in 5-10 % patients with sarcoidosis(2). Neurosarcoidosis should be considered in patients with known sarcoidosis who develop neurological complaints and in patients who present de novo with findings consistent with neurosarcoidosis. In this case series we present 4 cases of neurosarcoidosis with varied presentations.

CASE A:

A 35 year old man presented with insidious onset gradually progressive urinary urgency and incontinence for 1 year. He had associated erectile dysfunction for 6 months. He developed circumferential burning sensation over his trunk with a pulling pain in his left foot for 4 months. He also had numbness of left leg, stiffness and weakness for the last 4 months. He developed numbness and progressive weakness of right leg in the 20 days preceding admission.

At 26 years he had right sided Bell's palsy which resolved within one month. At 31 years of age he developed sudden onset of hearing loss in the right ear with pure tone audiometry showing profound sensori-neural hearing loss in right ear and moderate conductive hearing loss in left ear.

On examination he had sensori-neural hearing loss in the right ear. Both lower limbs were hypertonic with power of 4/5, brisk reflexes with bilateral extensor plantar responses. He also had ill-defined hyperasthesias below T 2 level. He had bilateral spastic gait with scissoring.

On investigation MRI dorso-lumbar spine showed ill-defined T2 hyperintensities in the central part of spinal cord extending from D7-D11 suggestive of transverse myelitis extending longitudinally over several segments of the spinal cord. Serum Aquaporin 4 levels and CSF oligoclonal bands were negative. His serum ACE levels were elevated 77 (Normal 40-52) and serum calcium was normal at 9.6 mg/dl.

He was treated with high dose intravenous steroids followed by oral Prednisolone. He was also started on Azathioprine as a steroid sparing agent. On follow up he was able to walk with the help of a walker.

CASE B:

A 23 year old male presented with painful sudden onset of diminution of vision in the right eye for past 5 months which progressed to complete loss of vision over a period of 5 days. He had diminution of vision in the left eye 2 weeks prior to admission. He had polyuria and polydypsia for one month.

On examination he had no perception of light in the right eye with relative afferent pupillary defect (RAPD) and primary optic atrophy. Left eye vision was 25/20. He did not have any other cranial nerve, motor, sensory or cerebellar involvement.

Investigations revealed normal CSF analysis. CSF PCR for mycobacterial DNA (GeneXpert) was negative. Serum ACE levels were normal. MRI Brain showed contrast enhancing soft tissue shadow on the right extending from the lateral wall of cavernous sinus to the orbital apex and superior orbital fissure with enhancement of pituitary gland. Dural thickening was noted in the right temporal region. ANA and ANCA (c and p) were negative. Chest X ray did not show any evidence of mediastinal lymphadenopathy.He had with central Diapetes insipidus in the form of polyuria(4L/day), polydypsia(5L/day) with normal serum osmolality and low urine osmolality.

He was treated with high dose intravenous steroids for 5 days followed by oral prednisolone. He was also started on T Desmopressin 0.1 mg per day. His diabetes insipidus resolved with oral Desmopressin but vision in right eye did not improve.

CASE C:

A 53 year male, a known diabetic for 10 years and hypertensive for one year presented with numbness over the left side of his scalp and face with double vision on left lateral gaze for 10 months. Five months ago he developed drooping of left upper eyelid. He also developed visual impairment in the right eye. Three months ago he developed deviation of the angle of the mouth to the left, difficulty in swallowing with nasal regurgitation of fluids and hoarseness of voice.

On examination he had reduced visual acuity,RAPD and optic atrophy in right eye. He had recovering 3rd cranial nerve palsy in left eye in the form of partial ptosis of the left eye with mild adduction and elevation restriction of eye movements. He also had right lower motor neuron facial palsy. Examination of higher mental functions, motor, sensory and cerebellum were normal.

On investigation MRI Brain showed meningeal enhancement in anterior temporal and right orbital apex area. CSF analysis was normal and there were no oligo-clonal bands. Serum Aquaporin 4 antibodies were negative. Serum ACE levels were elevated at 57 U/L. Serum calcium was 9.8 mg%. ANA and ANCA (c and p) were negative.He was treated with intravenous steroids followed by oral Prednisolone.

CASE D:

A 55 year old woman presented with difficulty in swallowing and nasal regurgitation of fluids for 3 weeks. She had hoarseness of voice. Both the swallowing difficulty and dysphonia worsened on repetitive performance. She did not have any diplopia, drooping of eyelids, limb weakness or respiratory complaints.

On examination she had inguinal and axillary lymphadenopathy. Examination showed bilateral palatel weakness with pooling of secretions. Motor examination revealed normal tone, power and reflexes. Direct Video Laryngoscopy revealed left vocal cord palsy.

Investigations showed greater than 10% decremental response on Repetitive nerve stimulation (RNS) in orbicularis oculi and nasalis muscles. Acetylcholine receptor antibodies were positive. CT chest

showed multiple lymph nodes in high mediastinal, upper and lower paratracheal, cervical areas, with left axillary lymph nodes measuring 1.9 X1.4 cm. MRI brain and CSF analysis were normal. Serum ACE levels were elevated (131 u/ml). Inguinal lymph node biopsy revealed complete effacement of architecture by multiple closely packed well-formed non caseating discrete granulomas composed of epitheloid histiocytes and Langhan type of giant cells, some of which were rimmed by lymphocytes and plasma cells, suggestive of sarcoidosis.

She improved dramatically with T Pyridostigmine and worsened on withdrawal. Improvement of bulbar palsy with pyridostigmine indicated co-existant myasthenia gravis.

DISCUSSION:

Sarcoidosis is a systemic inflammatory disorder mainly affecting skin, lungs, salivary glands lacrimal glands and lymphoid tissues including the spleen. The peak incidence of neurosarcoidis occurs in the 3rd to 5th decade(6). Women tend to present with sarcoidosis at a later age compared to men and are more likely to have neurosarcoidosis and systemic disease(7). In order to diagnose neurosarcoid there needs to be a high degree of suspicion. Not all CNS symptoms in a patient who is a known case of sarcoidosis should be attributed to neurosarcoidosis unless it is proved (2). Chronic infections such as tuberculosis or fungal infections secondary to immunosuppression used in the treatment of sarcoidosis and lympho-proliferative disorders which have a greater prevalence in sarcodosis may involve the nervous system and need to be excluded. Neurosarcoidosis can cause damage due to production of inflammatory cytokines, presence of intra-axial granulomas with mass effect and leptomeningeal involvement (2). Whenever possible sarcoidosis should be confirmed by biopsy. If the site of lesion is not amenable to biopsy, evidence of sarcoidosis should be sought in extra cranial sites(8).

The four cases we report here showed the varied presentations of neurosarcoisosis. There are some distinctive patterns of neurological involvement such as bilateral lower motor neuron facial nerve involvement, diabetes insipidus and primary optic atrophy which should alert one to this possibility. While histologic confirmation of the presence of non-caseating granulomata in multiple anatomical locations is the hall-mark of sarcoidosis, when patients present with isolated CNS involvement as in our patients A and B, getting histologic confirmation is risky in view of the critical anatomical locations of the lesions. In this situation it is necessary to take the overall picture into consideration along with corroborative evidence such as ACE levels and the exclusion of other possibilities by appropriate tests to arrive at a probable diagnosis and initiate treatment. Serum angiotensin-converting-enzyme (ACE) levels are elevated in only 25-35% of subjects with sarcoidosis and do not correlate with disease activity(2,9). CSF ACE levels have poor sensitivity (24-55%) and can be falsely positive in malignancy or infections(10). Overall an elevated serum ACE level would be an additional clue to the diagnosis of sarcoidosis but is neither sensitive nor specific. However it may be useful for follow up.

Cranial neuropathy is quite common affecting 54-75% subjects(6,10). Lower motor neuron facial nerve involvement is present in about 30% of patients with sarcoidosis. The facial paralysis can be either unilateral (2/3rd) or bilateral (in 1/3rd), simultaneous or sequential, or recurrent. Most recover spontaneously but occasional residual palsy may persist(8,11). Bilateral parotid enlargement with facial nerve palsy should make one suspect sarcoidosis as the etiologic factor. Facial nerve involvement was present in 2 of our 4 patients (patients A and C).

Optic nerve involvement as in our patient B occurs in up to 35% subjects and can be either unilateral or bilateral. It is interesting to note that on MR imaging of patients with neurosarcoidosis optic nerve is the cranial nerve which consistently shows contrast enhancement. Visual prognosis after optic neuropathy is poor even when treatment is instituted promptly (2).

Vestibulocochlear (8th cranial nerve) palsy can present as acute unilateral or bilateral hearing loss as in our patient A. Early treatment with steroids can result in partial recovery. Significant chronic hearing loss is not unusual with bilateral involvement(11,12).

Trigeminal (5th) nerve involvement can present with facial paresthesias, hyperasthesias or typical trigeminal neuralgias in 8-19% subjects with neurosarcoidosis(4). Our patient C had subjective sensory symptoms in the area of distribution of the left 5th cranial nerve but had no objective sensory loss.

Neuroendocrine dysfunction by way of involvement of the neuro and or adenohypophysis occurs in 14 % of patients with neurosarcoidosis. Direct hypothalamic involvement due to granulomatous inflammation of the hypothalamic-pituitary axis can lead to central diabetes insipidus as in patient B in the present series. Indeed in a case series of spontaneous diabetes insipidus from India 19 % of patients had sarcoidosis as the cause(13). Some patients with sarcoidosis have nephrogenic diabetes insipidus due to hypercalcemia. In sarcoid tissue activated macrophages which have unregulated 1 alpha hydroxylase activity secrete calcitriol (1, 25 dihydroxy cholecalciferol) which leads to intestinal calcium hyperabsorption and hypercalcemia. Adenohypophyseal involvement in neurosarcoidosis is less common and deficiency of anterior pituitary hormones to varying extents can lead to hypotension or hyponatremia due to cortisol deficiency, hypothyroid features and hypogonadism in both men and women. In women in addition galactorrhea, amenorrhea and hyperprolactinemia may occur (2). Radiological resolution of the lesion which occurs with treatment is not generally accompanied by recovery of hypothalamo-hypophyseal axis and most patients require life-long hormone replacement(10).

Spinal cord involvement occurs in 15% of patients with neurosarcoidosis. Neurosarcoidosis can present as a longitudinally extensive transverse myelitis in the cervico-thoracic portions of the spinal cord. The combination of longitudinally extending spinal cord lesion and optic nerves involvement as in our patient A may mimic neuromyelitis optica (NMO). In NMO Aquaporin 4 antibodies are usually positive. Therefore neurosarcoidosis should be considered as a differential diagnosis whenever Aquaporin 4 antibodies are negative in a patient with longitudinally extending spinal cord lesion(8). Isolated cauda equina involvement can present with bowel, bladder and sexual dysfunction(8). The saddle anesthesia and progressive asymmetric involvement of one lower limb after the other in our patient along with bladder and bowel involvement (loss of anal sphincter tone) were consistent with additional cauda equina lesion. Vague diffuse sensory loss with inconsistent or normal sensory findings due to the patchy and non-contiguous pattern of cord and leptomeningeal involvement is characteristic. Our patient had only a band of hyperesthesia corresponding to T2 segment. On contrast MRI persistent gadolinium enhancement even after treatment is highly suggestive of sarcoidosis. Since biopsy from the spinal cord is a high risk invasive procedure it should be reserved for those cases where no diagnosis has been found despite extensive search for other organ involvement(14). Prognosis of recovery from myelitis is poor(11).

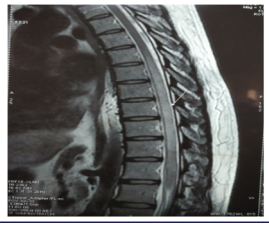
SUBACUTE-CHRONIC MENINGITIS (64%):

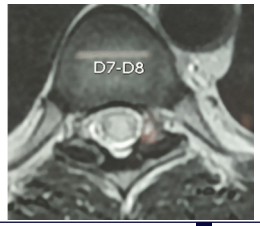
The dura and leptomeninges can be affected by acute or chronic inflammation. Subjects present with headache, fever and neck stiffness. Meningeal involvement can also lead on to the development of communicating hydrocephalus(10). CSF analysis may show pleocytosis with lymphocytic predominance and elevated protein(8).

The coexistence of myasthenia gravis and sarcoidosis though rare has been reported(15,16). Our patient D had fluctuating weakness and symptoms improved with Pyridostigmine and worsened on drug withdrawal. Her symptoms improved even long before starting steroids and this implies that myasthenia gravis rather than sarcoidosis caused her bulbar symptoms. The underlying pathophysiology in both disorders is T cell mediated autoimmunity(17). The coexistence can be purely coincidental considering the rarity of the association. However the possibility that the two disorders are part of a larger underlying autoimmune spectrum cannot be excluded.

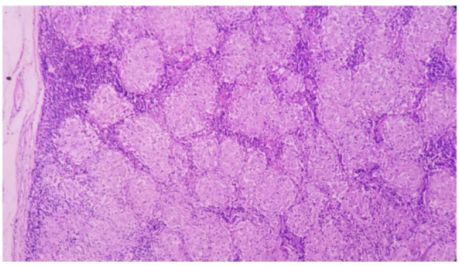
CONCLUSION:

The diagnosis of neurosarcoid is challenging because it is a great clinical and radiological mimic. Symptoms and signs are le light on etiology. A firm diagnosis should be based on biopsy confirmed presence of non caseating granulomas in multiple tissues with exclusion of other possible differentials. A high degree of suspicion is needed to diagnose neurosarcoidosis





Case A MRI Dorsolumbar spine: Illdefined T 2 hyperintensities in the central part of spinal cord extending from D7 to D11 levels-suggestive of transverse myelitis.



Case D Inguinal lymph node biopsy revealed complete effacement of architecture by multiple closely packed well-formed non caseating discrete granulomas composed of epitheloid histiocytes and Langhan type of giant cells, some of which were rimmed by lymphocytes and plasma cells, suggestive of sarcoidosis.

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